(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 May 2005 (19.05.2005)

PCT

(10) International Publication Number
WO 2005/044824 A2

(51) International Patent Classification[7]: C07D 501/00, A61P 31/00

(21) International Application Number: PCT/IB2004/003571

(22) International Filing Date: 1 November 2004 (01.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1368/DEL/2003 7 November 2003 (07.11.2003) IN

(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru Place, 110 019 New Delhi (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Yatendra** [IN/IN]; U-26/5, Phase-III, DLF Qutab Enclave, 122 001 Gurgaon, Haryana (IN). **PRASAD, Mohan** [IN/IN]; House No. P-3/3, Phase II, DLF Qutab Enclave, 122 001 Gurgaon, Haryana (IN). **SINGH, Kaptan** [IN/IN]; Flat No. B-02, Saket Enclave, Rajendra Nagar, Sahibabad, Ghaziabad, 201 005 Uttar Pradesh (IN). **PRASAD, Ashok** [IN/IN]; 147/9, Dr. Gupta's Flats, Kishangarh, Vasant Junj, New Delhi 110070 (IN). **RICHHARIYA, Santosh** [IN/IN]; Hous No. 26, Ganesh Ward, Bina District Sagar, 470 002 Madhya Pradesh (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay, R., 600 College Road East, Suite 2100, Princeton, NJ 08540 (IN).

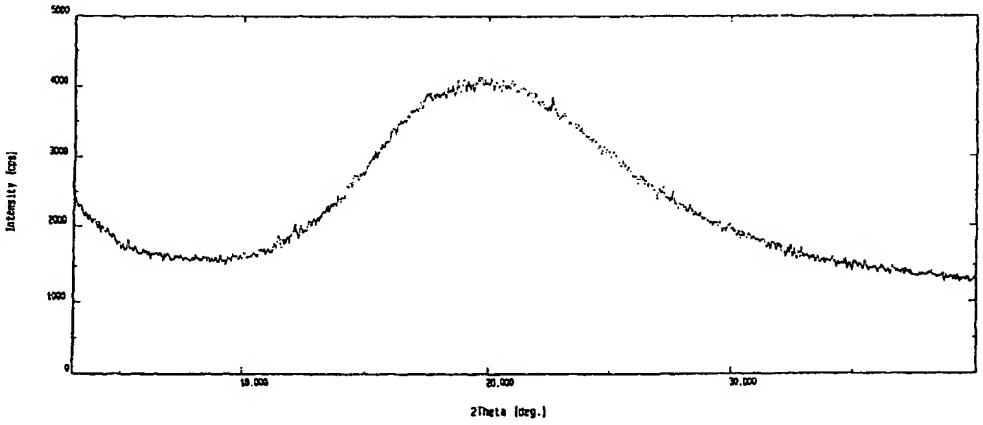
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: PROCESSES FOR THE PREPARATION OF HIGHLY PURE 3-(2-SUBSTITUTED VINYL) CEPHALOSPORIN



(57) Abstract: The present invention relates to a process for preparation of highly pure amorphous and crystalline forms of cefditoren pivoxil and pharmaceutical compositions comprising highly pure amorphous and crystalline forms of cefditoren pivoxil. The present invention also relates to a method of treating infections using highly pure amorphous and crystalline forms of cefditoren pivoxil. The highly pure cefditoren pivoxil has a purity greater than 98.5% and contains less than 1.0% of the E-isomer impurity and less than 1 % of the Δ^2isomer impurity.

WO 2005/044824 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

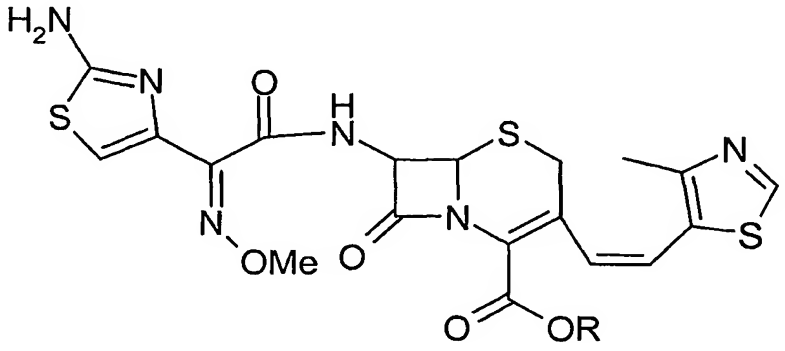
PROCESSES FOR THE PREPARATION OF HIGHLY PURE 3-(2-SUBSTITUTED VINYL) CEPHALOSPORIN

Field of the Invention

The present invention relates to processes for preparing highly pure amorphous and crystalline forms of 3-(2-substituted vinyl) cephalosporin. In particular, the present invention relates to processes for preparation of highly pure amorphous and crystalline forms of cefditoren pivoxil and pharmaceutical compositions comprising highly pure amorphous and crystalline forms of cefditoren pivoxil. The present invention also relates to methods of treating infections using highly pure amorphous and crystalline forms of cefditoren pivoxil.

Background of the Invention

Cefditoren pivoxil of Formula I (also known as ME-1207), which is a pivaloxymethyl



FORMULA I

ester of cefditoren (also known as ME-1206), is a third generation cephalosporin derivative belonging to the class of 3-(2-substituted vinyl) cephalosporin, which was first developed by Meiji Seika of Japan with the aim of producing active cephalosporins with potent and broad-spectrum activity (U.S. Patent No. 4,839,350). Cefditoren pivoxil is highly active, not only against a variety of gram-positive and gram-negative bacteria, but also against some resistant strains of bacteria. Cefditoren pivoxil of Formula I is chemically known as [6R-[3(Z),6a,7b(Z)]]-7-[[(2-Amino-4-

thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxy-methyl ester.

U.S. Patent No. 4,839, 350 describes a process for preparing amorphous form of cefditoren pivoxil. This process is disclosed as being non-selective and giving more than 20% of unwanted E-isomer, which is then separated by means of column chromatography. The purity of cefditoren pivoxil obtained is described as being typically around 94.0% to 95.5% when analyzed by HPLC.

U.S. Patent No. 6,294,669 describes a crystalline substance of cefditoren pivoxil and process for preparing the same. The crystalline substance is described as having a purity of about 97 to 98%, typically 97.7%, which is believed to be not sufficiently pure for incorporation into a pharmaceutical composition due to the high amount of impurities present. The disclosed process for converting amorphous cefditoren pivoxil to the crystalline substance is believed to be very complicated, requiring eight steps that include dissolution, concentration, and addition of two or three different solvents in different steps. Thus, the conversion of amorphous form to crystalline form may be time consuming, low yielding and difficult to scale up to commercial levels. In addition, the crystalline form of cefditoren pivoxil may not suitable for oral administration due to its poor solubility in water.

U.S. Patent No. 6,342,493 describes a process for preparing orally administrable compositions that include particles composed of a homogeneous mixture of a crystallographically stable, amorphous, water soluble substance of cefditoren pivoxil and a water soluble high molecular weight polymer. The process involves mixing crystalline cefditoren pivoxil and a water soluble, high molecular weight polymer in an acidic solution followed by basification of the acidic solution to precipitate a yellow-colored powdery composition that contains amorphous cefditoren pivoxil and high molecular weight polymer. Many technical problems are believed to exist in this process, such as the need for strict production controls and requirements to carry out the operation. Moreover, this process may not provide an amorphous product free from additives. Further, the use of the amorphous material containing the additives may be limited in pharmaceutical dosage forms.

Japanese Patent Application No. 2001-131071A2 describes a process for preparing amorphous cefditoren pivoxil by precipitation, spray-drying, and freeze-drying. Also described is a process of converting crystalline cefditoren pivoxil to amorphous cefditoren pivoxil by milling. This process provides a product that has purity in the range of 93 to 98%. For precipitation, spray drying and freeze-drying, no particular form of cefditoren pivoxil is reported. The crystalline form of cefditoren pivoxil has negligible solubility at the specified volume in the given solvents, suggesting that it is the amorphous form of cefditoren pivoxil that is used for spray-drying, freeze-drying or precipitation.

However, there remains a need for highly pure amorphous and crystalline forms of cefditoren pivoxil produced by a simple, cost-effective process that is easily scalable to commercial level.

Summary of the Invention

In one general aspect there is provided highly pure cefditoren pivoxil. The cefditoren pivoxil has a purity greater than 98.5% and contains less than 1.0% of the E-isomer impurity and less than 1% of the Δ^2-isomer impurity.

Embodiments of the compound may include one or more of the following features. For example, the compound may be in amorphous form. In amorphous form, the compound may have a XRD pattern as depicted in Figure I.

The compound may be in a crystalline form. In the crystalline form, the compound may have a XRD pattern as depicted in Figure II.

In another general aspect there is provided a process for preparing crystalline cefditoren pivoxil from amorphous cefditoren pivoxil. The process includes (a)(i) adding amorphous cefditoren pivoxil to an organic solvent optionally containing water and/or (ii) adding an organic solvent optionally containing water to amorphous cefditoren pivoxil; (b) crystallizing the product from the reaction mixture; and (c) isolating crystalline cefditoren pivoxil.

Embodiments of the process may include one or more of the following features or those described above. For example, the organic solvent may be one or more of an alcohol, a ketone, an ester, a cyclic ether, a nitrile, a glycol, a chlorinated hydrocarbon, or a mixture thereof. The alcohol may be one or more of ethanol, methanol, isopropyl

alcohol, n-butanol, iso-butanol, amyl alcohol or a mixture thereof. The ester may be one or more of ethyl formate, methyl acetate, ethyl acetate, isobutyl acetate, butyl acetate or a mixture thereof. The ketone may be one or more of acetone, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone or a mixture thereof. The cyclic ether may be one or more of tetrahydrofuran, 1,4-dioxane or a mixture thereof. The glycol may be one or more of propylene glycol, ethylene glycol or a mixture thereof. The chlorinated hydrocarbon may be one or more of methylene chloride, ethylene chloride, chloroform or a mixture thereof.

The organic solvent may contain about 0.01 to about 50% by weight of water. The reaction mixture may be stirred at a temperature of about –20°C to about 100°C to crystallize. The crystallization temperature may be kept in the range of about 0°C to about 60°C.

The cefditoren pivoxil obtained may be highly pure cefditoren pivoxil having a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

In another general aspect there is provided a process for preparing an amorphous form of cefditoren pivoxil from crystalline cefditoren pivoxil. The process includes: (a) dissolving crystalline cefditoren pivoxil in a first organic solvent; (b) adding a second organic solvent to the solution or adding the solution to the second organic solvent in optional order of succession to precipitate cefditoren pivoxil; and (c) isolating the amorphous cefditoren pivoxil from the reaction mixture.

Embodiments of the process may include one or more of the following features or those described above. For example, the first organic solvent may be at least one water-immiscible or partially miscible solvent. The at least one water-immiscible or partially miscible solvent may be an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof. The second organic solvent may be an alkyl ether, a hydrocarbon or a mixture thereof.

The cefditoren pivoxil obtained may be highly pure cefditoren pivoxil having a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

The dissolution of crystalline cefditoren pivoxil in the first organic solvent may be effected by initially dissolving crystalline cefditoren pivoxil in a third organic solvent. The third organic solvent may be one or more of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof.

In another general aspect there is provided a process for preparing an amorphous form of cefditoren pivoxil. The process includes the steps of: (a) dissolving crystalline cefditoren pivoxil in a first organic solvent; (b) removing the first organic solvent from the reaction mixture; and (c) isolating the amorphous form of cefditoren pivoxil.

Embodiments of the process may include one or more of the following features or those described above. For example, the first organic solvent may be at least one water-immiscible or partially miscible solvent. The at least one water-immiscible or partially miscible solvent may be an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof.

The process may further include applying heating to dissolve the crystalline form in the first organic solvent.

The first organic solvent may be removed under reduced pressure. The first organic solvent may be removed by spray-drying the solution of crystalline cefditoren pivoxil.

The cefditoren pivoxil obtained may be highly pure cefditoren pivoxil having a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

In another general aspect there is provided a process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline form. The process includes the steps of: (a) dissolving a crystalline form of cefditoren pivoxil in an organic solvent optionally containing water; and (b) freeze drying or lyophilizing the solution to get highly pure amorphous form of cefditoren pivoxil. The cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

Embodiments of the process may include one or more of the following features or those described above. For example, the organic solvent may be at least one water-immiscible or partially miscible solvent. The at least one water-immiscible or partially miscible solvent may be an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof.

The process may further include applying heating to dissolve the crystalline form in the organic solvent.

In another general aspect there is provided a process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline form. The process includes the steps of: (a) dissolving the crystalline cefditoren pivoxil in an acid, optionally in the presence of a water miscible organic solvent; (b) adding water to the solution in an amount sufficient to precipitate the cefditoren pivoxil from the solution; and (c) isolating the highly pure amorphous cefditoren pivoxil from the solution. The cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

Embodiments of the process may include one or more of the following features or those described above. For example, the acid may be at least one of an organic acid or an inorganic acid. The organic acid may be one or more of C1-12 alkyl or aryl carboxylic acids, C1-10 alkyl or aryl sulphonic acids or a mixture thereof. The C1-10 alkyl or aryl carboxylic acid may be one or more of formic acid, acetic acid, propionic acid, butyric acid, acrylic acid, benzoic acid, mono-, di- or trisubstituted benzoic acids, phenyl acetic acid, substituted phenyl acetic acid or a mixture thereof. The C1-12 alkyl or aryl sulphonic acid may be one or more of methanesulphonic acid, p-toluenesulphonic acid, benzenesulphonic acid or a mixture thereof.

The inorganic acid may be one or more of hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid or a mixture thereof. The acid may contains a water miscible organic solvent. The water miscible organic solvent may be one or more of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof.

In another general aspect there is provided a process for converting a mixture of the amorphous and crystalline forms of cefditoren pivoxil to highly pure amorphous form of cefditoren pivoxil. The mixture of amorphous and crystalline form of cefditoren pivoxil is prepared directly from the reaction mixture, from the crystalline form or from the amorphous form of cefditoren pivoxil and the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%. Embodiments of this process may include one or more of the features described above.

In another general aspect there is provided a pharmaceutical composition that includes a highly pure amorphous or crystalline form of cefditoren pivoxil and a pharmaceutically acceptable carrier. The cefditoren pivoxil is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

In another general aspect there is provided a method of treating infections caused by gram positive, gram negative and resistant strains of bacteria. The method includes administering to a mammalian host in need thereof a therapeutically effective amount of the highly pure amorphous or crystalline form of cefditoren pivoxil. The cefditoren pivoxil is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims. For example, some of the reactions described herein can be characterized as one pot reactions.

List of Figures

Figure I is an X-ray powder diffraction (XRD) pattern of highly pure amorphous form of cefditoren pivoxil.

Figure II is an X-ray powder diffraction (XRD) pattern of highly pure crystalline form of cefditoren pivoxil.

Figure III is an X-ray powder diffraction (XRD) pattern of a mixture of highly pure crystalline and amorphous cefditoren pivoxil.

Detailed Description of the Invention

The present invention provides highly pure amorphous cefditoren pivoxil having purity greater than 98.5% and containing less than 1.0% of the unwanted E-isomer impurity and less than 1% of the Δ^2-isomer impurity. Figure I shows an XRD pattern of the amorphous form of cefditoren pivoxil.

The term "highly pure cefditoren pivoxil," as used herein, refers to cefditoren pivoxil in amorphous or crystalline form having purity not less than 98.5% and containing less than 1.0% of the E-isomer impurity and less than 1% of the Δ^2-isomer impurity. More preferably the purity is not less than 99.0% which has less than 0.5% of E-isomer impurity and less than 0.5% of Δ^2-isomer impurity. Most preferably highly pure cefditoren pivoxil refers to cefditoren pivoxil having purity not less than 99.20% and containing less than 0.1% of E-isomer impurity and less than 0.5% of Δ^2-isomer impurity.

The present invention also provides a highly pure crystalline cefditoren pivoxil having purity greater than 98.5% and containing less than 1.0% of the unwanted E-isomer impurity and less than 1% of the Δ^2-isomer impurity. Figure II shows an XRD pattern of the crystalline form.

The present invention further provides an efficient, one-step process for preparing a crystalline form of cefditoren pivoxil from amorphous cefditoren pivoxil. The process includes the steps of:

a) adding amorphous cefditoren pivoxil to an organic solvent optionally containing water;

b) crystallizing the product from the reaction mixture; and

c) isolating crystalline cefditoren pivoxil.

Amorphous cefditoren pivoxil can be prepared according to the process described in copending PCT Application No. PCT/IB2004/002648, which is incorporated by reference herein in its entirety. The amorphous material can be added to an organic solvent optionally containing water or, alternatively, the organic solvent with optional water can be added to the amorphous material in an optional order of succession. The resultant reaction mixture thereafter can be stirred at a temperature of about -20 °C to about 100 °C to complete crystallization. The crystalline material can be isolated from the

reaction mixture by conventional methods known to one of ordinary skill in the art. The obtained crystalline form of cefditoren pivoxil typically exhibits an XRD pattern as depicted in Figure II.

Organic solvents used in preparing crystalline cefditoren pivoxil can be, for example, ethanol, methanol, isopropyl alcohol, n-butanol, iso-butanol, amyl alcohol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, acetone, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, acetonitrile, tetrahydrofuran, 1,4-dioxane, propylene glycol, ethylene glycol, methylene chloride, ethylene chloride, chloroform or mixtures thereof. The solvent can contain up to about 0.01 % to about 50 % by weight of water.

Typically, the crystallization temperature can be kept between about 0 °C to 60 °C. The isolated crystalline cefditoren pivoxil then can be optionally dried under vacuum to get highly pure cefditoren pivoxil having a purity greater than 98.5%, wherein the unwanted E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

The present invention also encompasses a process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline cefditoren pivoxil. The process includes the steps of:

a) dissolving crystalline cefditoren pivoxil in a first organic solvent;

b) adding a second organic solvent to the solution or adding the solution to the second organic solvent, in optional order of succession, to precipitate cefditoren pivoxil; and

c) isolating the amorphous cefditoren pivoxil from the reaction mixture.

The first organic solvent can be a water-immiscible or partially miscible solvent, including, for example, iso-butanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride, chloroform or a mixture thereof. The second organic solvent can be, for example, diisopropyl ether, diethyl ether, toluene, xylene, heptane, hexane, cyclohexane, cycloheptane, petroleum ether or a mixtures thereof. To enhance the precipitation, common techniques, for example, seeding with amorphous material or cooling the reaction mass, also can be effectively utilized. The

precipitated product then can be isolated from the reaction mass and dried under vacuum to get amorphous form of cefditoren pivoxil having purity greater than 98.5%, wherein the unwanted E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

The dissolution of crystalline cefditoren pivoxil in the first organic solvent can be effected by initially dissolving crystalline cefditoren pivoxil in a third organic solvent, for example, dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof. Water and a first organic solvent then can be added to this solution in optional order of succession to obtain a biphasic solution. The organic layer can be separated and washed successively with water to remove the traces of the third organic solvent. A solution of crystalline cefditoren pivoxil in first organic solvent can thus be effectively prepared.

The present invention also encompasses a process for preparing a highly pure amorphous form of cefditoren pivoxil in a method that include the steps of:

a) dissolving crystalline cefditoren pivoxil in a first organic solvent;

b) removing the solvent from the reaction mixture; and

c) isolating amorphous form of cefditoren pivoxil.

The first organic solvent can be a water-immiscible or partially miscible solvent, for example, iso-butanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride, chloroform or a mixture thereof. If required, optional heating can be utilized to dissolve the crystalline form completely in the first organic solvent.

Dissolution of crystalline cefditoren pivoxil in a first organic solvent can be effected by initially dissolving crystalline cefditoren pivoxil in a second organic solvent, for example, dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof. Water and the first organic solvent then can be added to this solution in optional order of succession to obtain a biphasic solution. The organic layer can be separated and washed successively

with water to remove the traces of the second organic solvent. A solution of crystalline cefditoren pivoxil in a first organic solvent can thus be effectively prepared.

The solvent can be concentrated under vacuum of about 100 mm to about 0.01 mm of Hg. In particular, the solvent can be removed by vacuum distillation of the solution with optional heating at a temperature of about 0 °C to 100 °C to effect faster removal of the solvent.

The solvent can also be removed by spray-drying the solution of crystalline cefditoren pivoxil using a spray-dryer. For purposes of spray-drying, for example, a suitable spray dryer is the mini-spray Dryer (Model: Buchi 190 Switzerland), which operates on the principle of nozzle spraying in a parallel flow, *i.e.*, the product is sprayed in the same direction as the drying gas flow. The drying gas can be air or inert gases, for example, nitrogen, argon or carbon dioxide. Preferably, the drying gas is nitrogen.

The present invention also provides a process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline form using the following steps:

a) dissolving a crystalline form of cefditoren pivoxil in an organic solvent optionally containing water; and

b) freeze drying or lyophilizing the solution to obtain a highly pure amorphous form of cefditoren pivoxil.

A solution of crystalline cefditoren pivoxil in organic solvent optionally containing water is prepared as described above. In particular, dissolution of crystalline cefditoren pivoxil in a suitable organic solvent can be effected by initially dissolving crystalline cefditoren pivoxil in a second organic solvent, for example, dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof. Water and the suitable organic solvent can be added to this solution in optional order of succession to obtain a biphasic solution. The organic layer can be separated and washed successively with water to remove the traces of the second organic solvent. A solution of crystalline cefditoren pivoxil in a suitable organic solvent can thus be effectively prepared.

The solution of cefditoren pivoxil then is freeze-dried by conventional techniques to obtain the amorphous cefditoren pivoxil. The amorphous form can then be dried under vacuum.

Another aspect of the invention encompasses a process for preparing highly pure amorphous form of cefditoren pivoxil from the crystalline form of cefditoren pivoxil. This process includes the following steps:

a) dissolving crystalline cefditoren pivoxil in an acid, optionally in presence of a water miscible organic solvent;

b) adding water to the solution, sufficient to precipitate cefditoren pivoxil out from the solution; and

c) isolating highly pure amorphous cefditoren pivoxil from the solution.

Crystalline cefditoren pivoxil can be dissolved in an acid optionally containing a water-miscible organic solvent to form a clear solution. The solution optionally can be treated with charcoal or clarified or filtered to remove foreign particulate matter. The solution also can be obtained by gently warming the mixture. Water can be added to the solution at a rate sufficient to slowly precipitate the cefditoren pivoxil. After complete addition of water, the mixture can be chilled or partially concentrated to remove the organic solvent. The separated amorphous form can then be filtered and dried as per the methods described earlier.

The acid can be an organic acid, for example, of C_{1-12} alkyl or aryl carboxylic acids, or C_{1-10} alkyl or aryl sulphonic acids (*e.g.*, formic acid, acetic acid, propionic acid, butyric acid, acrylic acid, benzoic acid, mono or di or tri substituted benzoic acids, phenyl acetic acid, substituted phenyl acetic acid, methanesulphonic acid, p-toluenesulphonic acid, benzenesulphonic acid and the like) or a mixture thereof. The acid can be an inorganic acid, for example, hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid and the like, or a mixture thereof.

The water miscible organic solvent can be, for example, dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof.

The present invention also provides a process for converting a mixture of amorphous and crystalline forms of cefditoren pivoxil to a highly pure amorphous form of cefditoren pivoxil. In this process, a mixture of the amorphous and the crystalline forms of cefditoren pivoxil can be prepared directly from the reaction mixture or from the crystalline form or from the amorphous form of cefditoren pivoxil by the process already described in the specification with little variations in reaction temperature, quantity of solvent, reaction time, spray-drying temperature, flow rate of inert gas during spray-drying and the like. The mixture of amorphous and crystalline cefditoren pivoxil is then converted to the amorphous form by any of the techniques already described in the above embodiments.

The present invention also relates to pharmaceutical compositions and dosage forms that include one or more highly pure amorphous and/or crystalline forms of cefditoren pivoxil. Such pharmaceutical compositions can be used as an antibacterial in the treatment of infections caused by gram positive, gram negative and resistant strains of bacteria. The pharmaceutical compositions of the present invention also can contain a pharmaceutically acceptable carrier.

The invention also relates to methods of treating infections caused by gram positive, gram negative and resistant strains of bacteria. The methods include administering to a mammalian host in need thereof a therapeutically effective amount of one or more highly pure amorphous and/or crystalline forms of cefditoren pivoxil.

Provided below are illustrative examples of the inventions described herein. The examples are provided for purposes of further explaining the inventions and are not intended to be limiting.

Examples

EXAMPLE 1: PREPARATION OF CEFDITOREN PIVOXIL (FORMULA I)

Iodomethyl pivalate (10 g) was added in one lot to a stirred mixture of cefditoren sodium (20 g) in DMF (120 mL) at –15 °C. The reaction mixture was stirred at about -10 °C to –15 °C for 60 min. Subsequently, the reaction mixture was quenched by pouring the reaction mixture into a solvent mixture of deionized water and ethyl acetate. The ethyl acetate layer was washed sequentially by water, 0.5% $NaHCO_3$ and 0.1% HCl, and finally

by water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure until the residual volume was about 100 mL.

This solution was slowly added to cyclohexane (600 mL) at ambient temperature and stirred for 30 min. The product was filtered under reduced pressure and dried under vacuum yielding cefditoren pivoxil.

Yield: 18.8 g, 78% (XRD as per Figure I showed it to be an amorphous material)

HPLC Purity: 98.36%

E-isomer of Cefditoren pivoxil: 0.14%

Δ^2-isomer: 0.76%

IR in KBr (cm -1): 2974, 2934, 1787, 1752, 1678, 1534, and 1369.

EXAMPLE 2: PREPARATION OF CRYSTALLINE CEFDITOREN PIVOXIL

Denatured spirit (150 mL) was added to the product obtained in Example 1 (15 g) and the heterogeneous mixture was stirred at about 30 °C to about 35 °C for about 2-3 hrs until crystallization was complete. The product was filtered under reduced pressure and dried under vacuum to yield crystalline cefditoren pivoxil.

Yield: 13.5 g (XRD as per Figure II showed it to be crystalline material)

HPLC Purity: 99.23%

E-Isomer of Cefditoren pivoxil: 0.08%

Δ^2-isomer: 0.41%

IR in KBr (cm -1): 2961, 1785, 1736, 1724, 1620, 1529, and 1372

EXAMPLE 3: PREPARATION OF CRYSTALLINE CEFDITOREN PIVOXIL

The product obtained in Example 1 (2.0 g) was suspended in aqueous ethanol (90% v/v, 20 mL) at about 30–32 °C for 3.0 hrs to complete crystallization. The crystalline product was filtered and washed with aqueous ethanol (90%v/v, 5 mL) and dried at about 35–40 °C under vacuum to yield crystalline cefditoren pivoxil.

Yield: 1.7 g (XRD as per Figure II showed it to be crystalline material)

HPLC Purity: 98.61%

E-isomer of cefditoren pivoxil: 0.086%

Δ^2-isomer: 0.82%

IR in KBr (cm -1): 2961, 1785, 1736, 1724, 1620, 1529, 1372

EXAMPLE 4: PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline cefditoren pivoxil (2.0 g) was dissolved in DMF (10 mL) at ambient temperature. This solution was added to pre-cooled ethyl acetate at about 0–5 °C. The solution was washed with water three times and the ethyl acetate was concentrated under reduced pressure to yield a solution of cefditoren pivoxil. This solution was added slowly to cyclohexane (60 mL) over 10–15 minutes at ambient temperature and stirred for 60 minutes. The solid was filtered to yield amorphous cefditoren pivoxil.

HPLC Purity: 98.90%

E-Isomer of Cefditoren pivoxil: 0.15%

Δ^2-isomer: 0.69%

XRD as per Figure I showed it to be an amorphous material

EXAMPLE 5: PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline cefditoren pivoxil (20.0 g) was dissolved in DMF (100 mL) at ambient temperature. This solution was added to a pre-cooled mixture of ethyl acetate (600 mL) and water (400 mL) at about 5–10 °C. The resultant mixture was stirred for about 10-15 minutes and the layers were separated. The solution was subjected to spray-drying using a mini spray-dryer (Buchi Model 190) having an inlet temperature of about 75 °C and an outlet temperature of about 55 °C with a feed rate of 15 mL per minute. Cefditoren pivoxil (15 g) was thus obtained in an amorphous form.

HPLC Purity: 99.04%

E-Isomer of Cefditoren pivoxil: 0.10%

Δ^2-isomer: 0.60%

XRD as per Figure I showed it to be an amorphous material.

EXAMPLE 6: PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline Cefditoren pivoxil (5.0 g) was dissolved in DMF (30 mL) at ambient temperature. This solution was added to a pre-cooled mixture of ethyl acetate (150 mL) and water (100 mL) at about 5–10°C. The resultant mixture was stirred for about 10 to 15 minutes and the layers were separated. The organic layer was treated with activated charcoal and the mixture was filtered. The clear filtrate was concentrated under reduced pressure at about 10-15 °C to yield a foam. The traces of solvent were removed by vacuum distillation at about 20-25°C and at about 5-10 mm of Hg to yield amorphous cefditoren pivoxil 4.0 g).

HPLC Purity: 98.79%

E-Isomer of Cefditoren pivoxil: 0.13%

Δ^2-isomer: 0.59%

XRD as per Figure I showed it to be an amorphous material

EXAMPLE 7: PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Step A: Preparation of mixture of crystalline and amorphous cefditoren pivoxil from crystalline cefditoren pivoxil

Crystalline cefditoren pivoxil (2.0 g) was dissolved in acetic acid (4.0 mL) at ambient temperature. This solution was added to pre-cooled water (60 mL) at about 5–10°C. The resultant mixture was stirred for about 10 to 15 minutes at about 5-10 °C. The separated solids were filtered and washed with a copious amount of water. The product was then dried to yield a mixture of crystalline and amorphous cefditoren pivoxil (1.7 g).

Step B: Conversion of mixture of crystalline and amorphous cefditoren pivoxil to amorphous cefditoren pivoxil

The product obtained in Step A (1.7 g) was dissolved in DMF (10 mL) at ambient temperature. This solution was added to a pre-cooled mixture of ethyl acetate (50 mL) and water (35 mL) at about 5–10 °C. The resultant mixture was stirred for about 10 to 15 minutes and the layers were separated. The organic layer obtained was subjected to spray drying using a mini spray-dryer (Buchi Model 190) at an inlet temperature of about 75 °C and an outlet temperature of about 55 °C with a feed rate of 15 mL per minute. Cefditoren pivoxil (1.45 g) was thus obtained in an amorphous form.

HPLC Purity: 98.64%

E-Isomer of Cefditoren pivoxil: 0.10%

Δ^2-isomer: 0.75%

XRD as per Figure I showed it to be an amorphous material.

While the present inventions have been described in terms of their specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present inventions.

We claim:

1. Highly pure cefditoren pivoxil, wherein the cefditoren pivoxil has a purity greater than 98.5% and contains less than 1.0% of E-isomer impurity and less than 1% of Δ^2-isomer impurity.

2. The compound according to claim 1, wherein the compound is in an amorphous form.

3. The compound according to claim 2, wherein the compound has a XRD pattern as depicted in Figure I.

4. The compound according to claim 1, wherein the compound is in a crystalline form.

5. The compound of claim 4, wherein the compound has a XRD pattern as depicted in Figure II.

6. A process for preparing crystalline cefditoren pivoxil from amorphous cefditoren pivoxil, the process comprising:

   a) (i) adding amorphous cefditoren pivoxil to an organic solvent optionally containing water and/or (ii) adding an organic solvent optionally containing water to amorphous cefditoren pivoxil;

   b) crystallizing the product from the reaction mixture; and

   c) isolating crystalline cefditoren pivoxil.

7. The process according to claim 6, wherein the organic solvent is one or more of an alcohol, a ketone, an ester, a cyclic ether, a nitrile, a glycol, a chlorinated hydrocarbon, or a mixture thereof.

8. The process according to claim 7, wherein the alcohol is one or more of ethanol, methanol, isopropyl alcohol, n-butanol, iso-butanol, amyl alcohol or a mixture thereof.

9. The process according to claim 7, wherein the ester is one or more of ethyl formate, methyl acetate, ethyl acetate, isobutyl acetate, butyl acetate or a mixture thereof.

10. The process according to claim 7, wherein the ketone is one or more of acetone, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone or a mixture thereof.

11. The process according to claim 7, wherein the cyclic ether is one or more of tetrahydrofuran, 1,4-dioxane or a mixture thereof.

12. The process according to claim 7, wherein the glycol is one or more of propylene glycol, ethylene glycol or a mixture thereof.

13. The process according to claim 7, wherein the chlorinated hydrocarbon is one or more of methylene chloride, ethylene chloride, chloroform or a mixture thereof.

14. The process according to claim 7, wherein the organic solvent contains about 0.01 to about 50% by weight of water.

15. The process according to claim 6, wherein the reaction mixture is stirred at a temperature of about –20°C to about 100°C to crystallize.

16. The process according to claim 6, wherein the crystallization temperature is kept in the range of about 0°C to about 60°C.

17. The process according to claim 6, wherein the cefditoren pivoxil obtained is highly pure cefditoren pivoxil having a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

18. A process for preparing an amorphous form cefditoren pivoxil from crystalline cefditoren pivoxil, the process comprising:

a) dissolving crystalline cefditoren pivoxil in a first organic solvent;

b) adding a second organic solvent to the solution or adding the solution to the second organic solvent in optional order of succession to precipitate cefditoren pivoxil; and

c) isolating the amorphous cefditoren pivoxil from the reaction mixture.

19. The process according to claim 18, wherein the first organic solvent is at least one water-immiscible or partially miscible solvent.

20. The process according to claim 19, wherein the at least one water-immiscible or partially miscible solvent is an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof.

21. The process according to claim 18, wherein the second organic solvent is an alkyl ether, a hydrocarbon or a mixture thereof.

22. The process according to claim 18, wherein the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

23. The process according to claim 18, wherein the dissolution of crystalline cefditoren pivoxil in the first organic solvent is effected by initially dissolving crystalline cefditoren pivoxil in a third organic solvent.

24. The process according to claim 23, wherein the third organic solvent is one or more of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof.

25. A process for preparing an amorphous form of cefditoren pivoxil, the process comprising the steps of:

a) dissolving crystalline cefditoren pivoxil in a first organic solvent;

b) removing the first organic solvent from the reaction mixture; and

c) isolating the amorphous form of cefditoren pivoxil.

26. The process according to claim 25, wherein the first organic solvent is at least one water-immiscible or partially miscible solvent.

27. The process according to claim 26, wherein the at least one water-immiscible or partially miscible solvent is an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof.

28. The process according to claim 26, further comprising applying heat to dissolve the crystalline form in the first organic solvent.

29. The process according to claim 26, wherein the first organic solvent is removed under reduced pressure.

30. The process according to claim 26, wherein the first organic solvent is removed by spray-drying the solution of crystalline cefditoren pivoxil.

31. The process according to claim 25, wherein the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

32. A process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline form which comprises the steps of:

a) dissolving a crystalline form of cefditoren pivoxil in an organic solvent optionally containing water; and

b) freeze drying or lyophilizing the solution to get highly pure amorphous form of cefditoren pivoxil, wherein the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

33. The process according to claim 32, wherein the organic solvent comprises at least one water-immiscible or partially miscible solvent.

34. The process according to claim 33, wherein the at least one water-immiscible or partially miscible solvent is an alcohol, a ketone, an ester, a chlorinated hydrocarbon or a mixture thereof.

35. The process according to claim 32, further comprising applying heating to dissolve the crystalline form in the organic solvent.

36. A process for preparing a highly pure amorphous form of cefditoren pivoxil from crystalline form, the process comprising the steps of:

a) dissolving the crystalline cefditoren pivoxil in an acid, optionally in the presence of a water miscible organic solvent;

b) adding water to the solution in an amount sufficient to precipitate the cefditoren pivoxil from the solution; and

c) isolating the highly pure amorphous cefditoren pivoxil from the solution, wherein the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a

purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

37. The process according to claim 36, wherein the acid is at least one of an organic acid or an inorganic acid.

38. The process according to claim 37, wherein the organic acid is one or more of C_{1-12} alkyl or aryl carboxylic acids, C_{1-10} alkyl or aryl sulphonic acids or a mixture thereof.

39. The process according to claim 38, wherein the C_{1-10} alkyl or aryl carboxylic acid is one or more of formic acid, acetic acid, propionic acid, butyric acid, acrylic acid, benzoic acid, mono-, di- or trisubstituted benzoic acids, phenyl acetic acid, substituted phenyl acetic acid or a mixture thereof.

40. The process according to claim 38, wherein the C_{1-12} alkyl or aryl sulphonic acid is one or more of methanesulphonic acid, p-toluenesulphonic acid, benzenesulphonic acid or a mixture thereof.

41. The process according to claim 37, wherein inorganic acid is one or more of hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid or a mixture thereof.

42. The process according to claim 36, wherein the acid contains a water miscible organic solvent.

43. The process according to claim 42, wherein water miscible organic solvent is one or more of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or a mixture thereof.

44. A process for converting a mixture of the amorphous and crystalline forms of cefditoren pivoxil to highly pure amorphous form of cefditoren pivoxil, wherein the mixture of amorphous and crystalline form of cefditoren pivoxil is prepared directly from the reaction mixture, from the crystalline form or from the amorphous form of cefditoren pivoxil and the cefditoren pivoxil obtained is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

45. A pharmaceutical composition comprising a highly pure amorphous or crystalline form of cefditoren pivoxil and a pharmaceutically acceptable carrier, wherein the cefditoren pivoxil is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

46. A method of treating infections caused by gram positive, gram negative and resistant strains of bacteria comprising administering to a mammalian host in need thereof a therapeutically effective amount of the highly pure amorphous or crystalline form of cefditoren pivoxil, wherein the cefditoren pivoxil is highly pure cefditoren pivoxil and has a purity greater than 98.5%, the E-isomer is less than 1.0% and the Δ^2-isomer impurity is less than 1%.

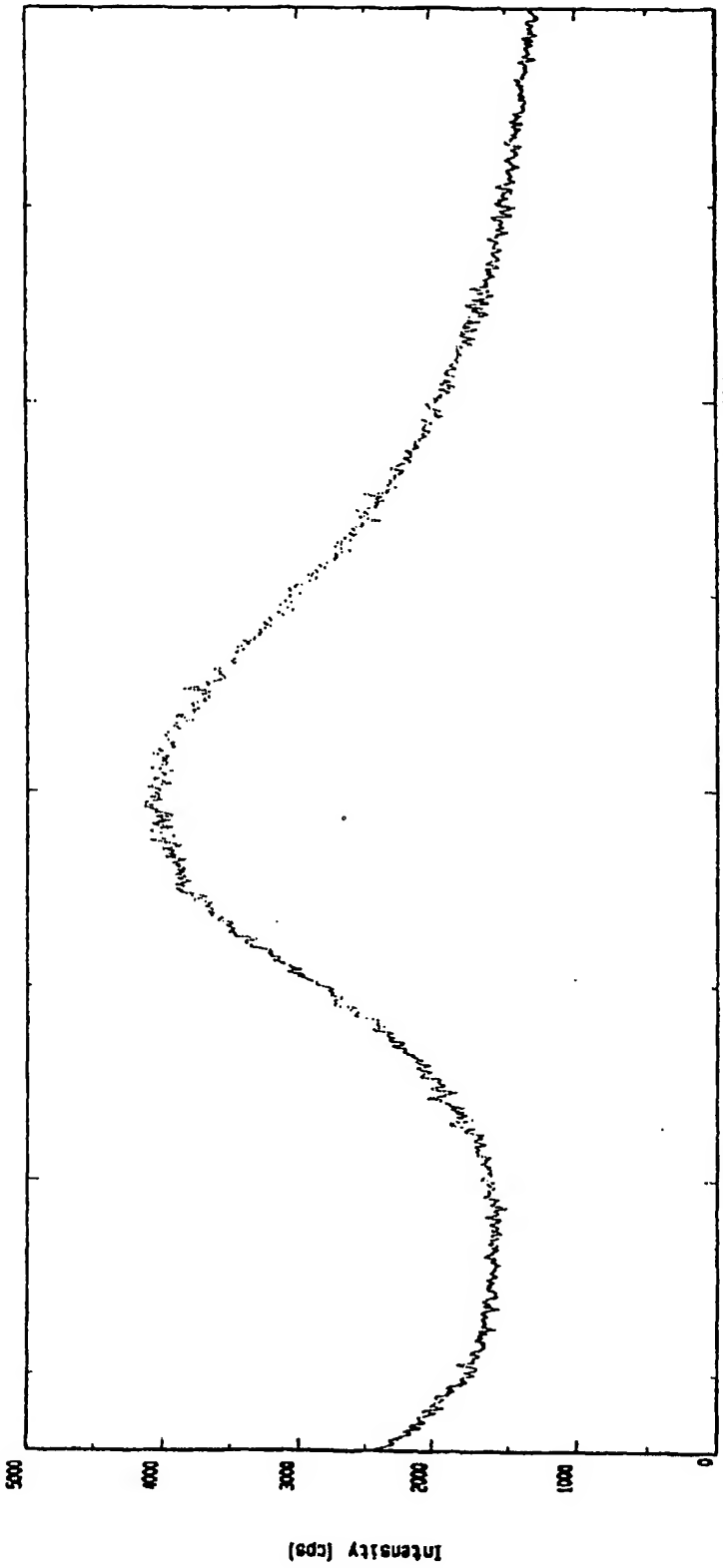

Intensity [cps]
5000
4000
3000
2000
1000
0
10.000
20.000
30.000
2Theta [deg.]

FIGURE 1

FIGURE 2

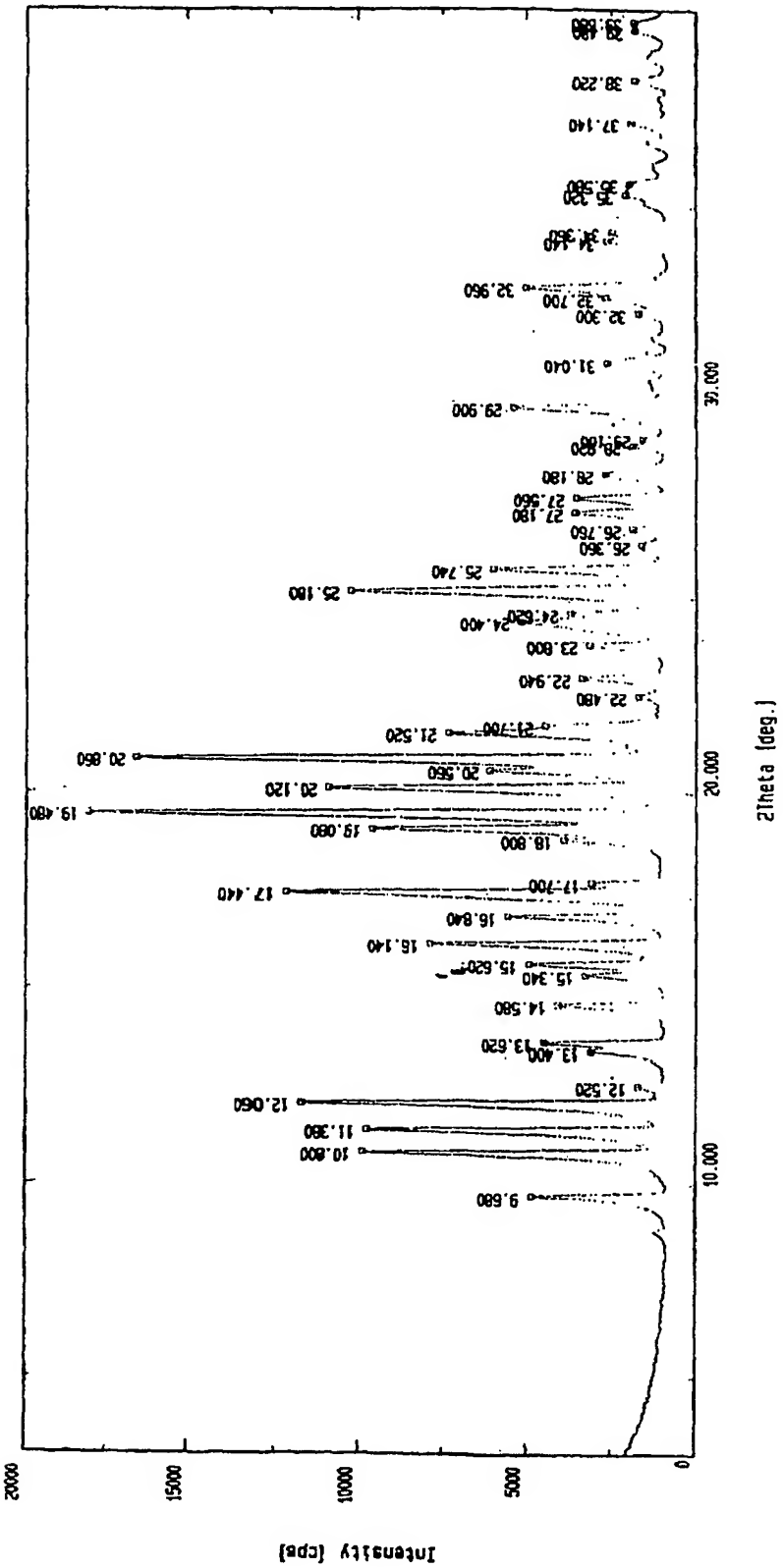
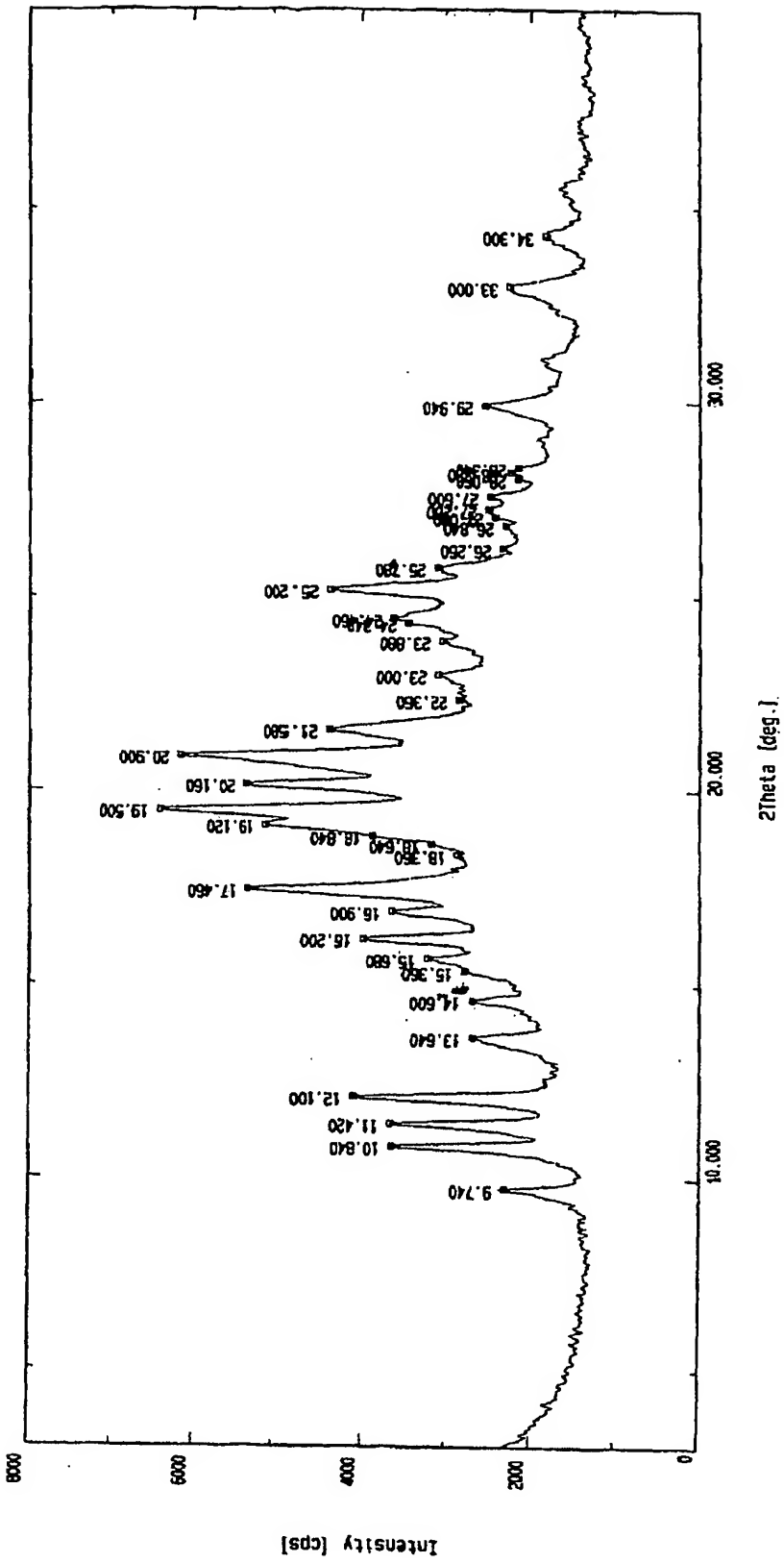

Intensity [cps]
20000
15000
10000
5000
0
2Theta [deg.]
30.000
20.000
10.000
9.680
10.800
11.360
12.060
12.520
13.400
13.620
14.580
15.340
15.620
16.140
16.840
17.440
17.700
18.800
19.080
19.480
20.120
20.560
20.860
21.520
21.700
22.480
22.940
23.800
24.400
24.620
25.180
25.740
26.360
26.760
27.180
27.360
28.180
28.820
29.160
29.900
31.040
32.300
32.700
32.960
34.140
34.360
35.320
35.560
37.140
38.220
38.680

FIGURE 3


Intensity [cps]
8000
6000
4000
2000
0
2Theta [deg.]
30.000
20.000
10.000
34.300
33.000
29.940
26.260
25.780
25.200
23.860
23.000
22.360
21.580
20.900
20.160
19.500
19.120
18.840
18.640
18.360
17.460
16.900
16.200
15.680
15.360
14.600
13.640
12.100
11.420
10.840
9.740